Claims 1 to 39 have also been provisionally rejected for double patenting with respect to the claims of co-pending Application No. 09/654,996. A terminal disclaimer is filed herewith to overcome this rejection.

Claims 1 to 39 have also been provisionally rejected for double patenting with respect to the claims of co-pending Application No. 09/749,189. A terminal disclaimer is filed herewith to overcome this rejection.

Claims 1 to 39 have also been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,015,557 to Tobinick et. al. This patent discloses the use of various routes of administration to deliver the TNF antagonists of consideration here to the systemic circulation, therby achieving a therapeutic response.

The novel routes of administration disclosed in this application are all routes of anatomically localized administration, including perilesional and intralesional routes. These routes are different than the routes designed for systemic administration, in many important ways.

First, localized anatomic administration (LAA) produces a higher concentration of the drug at the site of pathology. Systemic administration causes the drug to be diluted; LAA bathes the site of pathology in a high concentration of the unmodified drug. This factor alone can produces a more substantial therapeutic effect. In fact, there are clinical circumstances when the therapeutic effect requires high concentrations of drug; in these circumstances

systemic administration are completely ineffective, but LAA is effective. This is a concentration effect.

Second, LAA allows the unmodified drug to reach the site of pathology. This is critical difference, because systemic administration allows the drug to pass through the hepatic circulation. The liver is well known to function as a site of drug metabolism. Enzymes in the liver modify drugs, through the cytochrome P450 and other enzyme systems. These modifications can alter the structure and/or function of the drug.

Third, systemic circulation can lead to further alterations in the drug, either by degradation, hepatic or renal elimination, mechanical degradation, or other mechanisms of alteration, such as by the action of endothelial enzymes present within the vascular or lymphatic system.

Therefore, the novel routes of LAA of consideration in this patent application, including the intralesional and perilesional routes of administration and drug delivery, are distinguishable from systemic administration.

Finally, the inventor has treated a patient in whom the conventional subcutaneous route of administration of etanercept failed to result in therapeutic benefit for his low back pain condition. This patient was treated with the novel perilesional method of etanercept administration and he experienced dramatic therapeutic benefit. The theoretical benefits of LAA are thereby supported by this practical demonstration.

For these reasons, claims 1 to 39 of the present application patentably distinguish over U.S. Patent No. 6,015,557.

Claims 1 to 39 have also been rejected under 35 U.S.C. 103(a) and 102(e) as being unpatentable over U.S. Patent No. 6,015,557. For the reasons stated above, claims 1 to 39 of the Present application patentably distinguish over U.S. Patent No. 6,015, 557.

Alexander Patent

Claims 1 to 39 have also been rejected under 35 U.S. C. 103(a) as being unpatentable over U.S. Patent No. 6,180,355 to Alexander. The Alexander patent is entitled "Method for diagnosing and treating chronic pelvic pain syndrome." This patent concerns the diagnosis and treatment of chronic prostatitis/chronic pelvic pain syndrome, abbreviated CPPS by the author. "CPPS is the third of four subgroups of prostatitis recognized by the NIH," as stated in the patent.

The claims in the Alexander patent are limited to:

> "A method for diagnosing chronic pelvic pain syndrome or non-bacterial prostatitis. . ." or "A method for diagnosing a condition in a subject, wherein said condition is associated with elevated levels of GM-CSF." There is a brief mention within the body of the patent of the use of etanercept and other anti-tnf agents.

No claim is made in the present application regarding the use of TNF antagonists for the treatment of chronic prostatitis, non-bacterial prostatitis, or any related conditions.

It is well-known that TNF antagonists are useful for treating certain diseases which are unrelated to the neurological disorders claimed in the present application. Etanercept is FDA approved for the treatment of rheumatoid arthritis; this does not mean that it is obvious that it can be used for disorders of other organ systems. The fact that Alexander claims the use of etanercept for the treatment of conditions of the prostate in men does not make it obvious that it can be used to treat neurological conditions.

Additionally, the novel methods of treatment and routes of administration (LAA) claimed in the present application and discussed above in detail are not disclosed in the Alexander patent.

Additionally, while there is some discussion of the use of agents to inhibit the production of TNF in the Alexander patent, this is not the method claimed in this application. The methods claimed herein have an effect on the binding of already produced TNF molecules. The agents in Alexander have no effect on TNF secretion in already produced TNF molecules. These agents have no effect on TNF secretion.

For all of these reasons, the claims of the present application patentably distinguish over Alexander and should be allowed. As this application is now in condition for allowance, such action is respectfully requested.

Respectfully submitted,

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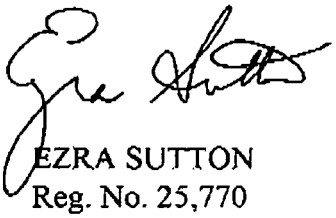

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